Remarks

Claims 1-21 are currently pending in the application. Claims 6 and 7 were elected with traverse for further prosecution. Claims 6 and 7 were rejected under 35 U.S.C. § 103(a). Applicants respectfully submit that all pending claims are patentable over the cited prior art for the reasons set forth below

1. Objections to the Specification

The Specification was objected to due to informalities on page 14, line 9. The Specification has been amended as required.

The Specification was objected to under 35 U.S.C. 112 first paragraph as allegedly failing to provide an enabling disclosure. The Specification has been amended to adequately teach how to use the invention.

2. Rejection of Claims 6 and 7 under 35 U.S.C. 112 First Paragraph

The Examiner rejected claims 6 and 7 under 35 U.S.C. 112 First Paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains. The claims have been amended to recite a detection kit comprising primary antibodies specific for 6-keto-prostoglandin $F_{1\alpha}$ and a 6-keto- $PGF_{1\alpha}$-aequorin conjugate and a secondary immunoglobulin antibody. Support for this amendment is found on pages 14 and 15 of the Specification. It is respectfully submitted that this amendment to the Claims and Specification renders the rejection moot.

3. Rejection of Claims 6 and 7 under 35 U.S.C. 112 Second Paragraph

The Examiner rejected claims 6 and 7 under 35 U.S.C. 112 Second Paragraph as allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention. Specifically the Examiner asserted that the interrelationships of the components was not clear. The claims have been amended to recite a detection kit comprising primary antibodies specific for 6-keto-prostoglandin $F_{1\alpha}$ and a 6-keto- $PGF_{1\alpha}$-aequorin conjugate and a secondary immunoglobulin antibody. Support for this amendment is found on pages 14 and 15 of the Specification. It is respectfully submitted that this amendment to the Claims renders the rejection moot.

4. Rejection of Claim 6 under 35 U.S.C. 103 (a) over Pradelles et al. in view of Kosak or Stults or Liotta.

The Examiner rejected claim 6 as allegedly being unpatentable over Pradelles et al. (Anal. Chem. 57: 1170, 1985) in view of Kosak or Stults or Liotta. Applicants respectfully disagree. First and foremost, Applicants respectfully assert that Pradelles fails to teach or disclose a kit for measuring prostacyclin in plasma. Pradelles merely teaches a method to couple pure acetylcholine esterase to 6-keto- $PGF_{1\alpha}$ As such, Pradelles fails to teach or disclose a kit for measuring amount of prostacyclin in plasma as claimed in the instant application.

Moreover, the Examiner concedes that Pradelles fails to explicitly or inherently teach aequorin labeling, and relies on Kosak (US 4,604,364), Stults (US 5,486,455), or Liotta et al. (US 5,942,407) to disclose an aequorin label.

Claim 6 recites a kit for measuring amount of prostacyclin in plasma comprising a 6-keto- $PGF_{1\alpha}$ -aequorin conjugate; an anti-6-keto- $PGF_{1\alpha}$ primary antibody; and a secondary immunoglobulin antibody. Neither Kosak, Stults or Liotta discloses a kit in comprising an anti-6-keto- $PGF_{1\alpha}$.aequorin conjugate.

It is argued by the Examiner that it would have been obvious to one having ordinary skill in the art at the time of invention to have substituted an alternative label such as aequorin for the enzyme label disclosed by Pradelles. Applicants respectfully disagree.

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A)The claimed invention must be considered as a whole;
(B)The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(C)The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(D)Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

It is well known to those skilled in the art, that attachment of a ligand to a protein may not result in an active conjugate. Moreover, the ability of a photoprotein to emit bioluminescence when a ligand is attached to it may be decreased, enhanced, or extinguish the bioluminescent activity completely. There is no way to predict what conjugation of a ligand molecule will do to the three dimensional structure of the protein and how the structure/activity

and stability will be affected. This is because the 6-keto- $PGF_{1\alpha}$ is hydrophobic and once attached could have interacted with the amino acids on the surface of the protein or on the active site where the chromophore resides and altered their H-bonding interactions and other types of electronic and hydrophobic interactions.

Thus, conjugation of a relatively hydrophobic molecule such as 6-keto- $PGF_{1\alpha}$ directly to the protein may have resulted in a non-bioluminescent aequorin conjugate and there was no reasonable expectation of success.

Absent disclosure of successful conjugation, it would not have been obvious to perform this conjugation.

Moreover, the 6-keto- $PGF_{1\alpha}$ -aequorin conjugate as disclosed in the instant application was bound tightly to the antibody chosen for the development of the immunoassay. There is no way to predict this either as those having ordinary skill in the art would not know whether a ligand in solution would bind to an antibody in the same manner as would a ligand conjugated to a protein. Conjugation of the ligand could render the ligand unable to bind to an antibody. In the instant case, the 6-keto- $PGF_{1\alpha}$ -aequorin conjugate was able to recognize the antibody in a strong enough manner that would allow for the detection of 6-keto- $PGF_{1\alpha}$ in plasma levels. In addition, the assay disclosed in the instant application consisting of using the 6-keto- $PGF_{1\alpha}$ -aequorin conjugate and its antibody, showed no cross-reactivity when binding to a series of compounds that are related in structure to 6-keto- $PGF_{1\alpha}$. This is not an obvious result when developing biological assays of the this type.

5. Rejection of Claim 7 under 35 U.S.C. 103 (a) over Pradelles et al. in view of Kosak or Stults or Liotta, and further in view of Lewis et al.

Claim 7 was rejected by the Examiner as allegedly being unpatentable under 35 U.S.C. 103 (a) over Pradelles et al., in view of Kosak or Stults or Liotta, and further in view of Lewis et al. Applicants respectfully disagree.

The Examiner concedes that neither Pradelles, Kosak, Stults or Liotta disclose a kit wherein the 6-keto- $PGF_{1\alpha}$ -aequorin conjugate comprises a cysteine free aequorin mutant.

The Examiner relies on Lewis et al., as reciting a cysteine free aequorin mutant and then asserts that it would have been obvious to substitute the aequorin mutant in the assay of Pradelles. Applicants respectfully traverse this rejection.

Lewis et al., discloses a, aequorin mutant , however, Lewis fails to disclose conjugating the mutant aequorin with 6-keto- $PGF_{1\alpha}$ as disclosed in the instant application.

Furthermore, as discussed above in reference to claim 6, it would not have been obvious to conjugate the 6-keto- $PGF_{1\alpha}$ molecule directly to the aequorin photo-protein and obtain a bioluminescent protein to be used in the development of an immunoassay.

6. New Claim 21

New Claim 21 discloses a kit wherein the cysteine free aequorin mutant comprises a unique cysteine residue introduced at amino acid 69, 70, 74 or 76, wherein the anti-6-keto $PGF_{1\alpha}$-aequorin conjugate is bound to the sulfhydryl group of cysteine. None of the prior art references disclose such a feature.

Applicants submit that the foregoing fully addresses the current rejection and removal thereof is respectfully requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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